The Long-Term Course of Functional and Anatomical Recovery After Macular Hole Surgery

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PURPOSE. To investigate the long-term effect of macular hole surgery, foveal structure and the thickness of retinal layers were analyzed with spectral-domain optical coherence tomography (SD-OCT). The long-term postoperative course of macular thickness and best-corrected visual acuity (BCVA) were followed.

METHODS. In a retrospective cohort study, SD-OCT scans were obtained from the horizontal midline in 51 eyes 54 ± 20 months postoperatively and from 30 control eyes. Retinal layer thickness was measured with a manual segmentation procedure aided by a customized computer program. BCVA was followed and macular thickness was quantified over time with the time-domain (TD) OCT Fast Macular Thickness program for up to 91 months.

RESULTS. Median foveal thickness between the outer plexiform and ganglion cell layers was greater than normal while that of the other retinal layers was normal. The median foveal shape remained slightly distorted. The postoperative decrease of central macular thickness toward normal values was delayed to 28 months postoperatively. Nasal macular thickness was decreased to normal at 6 months while superior, temporal, and inferior macular thickness was decreased to normal at 1 to 2 months postoperatively. Preoperative mean BCVA was 20/100 ± 3 lines. Postoperatively, mean BCVA was 20/44 ± 2 lines at 3 to 6 months, 20/40 ± 2 lines at 1 year, 20/32 ± 2 lines at 2 years, and 20/28 ± 1 line after a mean follow-up period of 54 ± 20 months.

CONCLUSIONS. Long-term postoperatively, the median thickness of retinal layers remains slightly thickened between the outer plexiform and the ganglion cell layer. The process of gradual recovery may continue for several years after macular hole surgery.

Keywords: macular hole, optical coherence tomography, retinal layers
were tested at the Department of Ophthalmology of the University Medical Center Schleswig-Holstein in Kiel, Germany. The tenets of the Declaration of Helsinki were followed. All subjects had given written informed consent to the surgical and the study procedures. Approval was obtained from the Institutional Review Board of the University Medical Center Schleswig-Holstein in Kiel, Germany. All subjects were pseudophakic with clear optical media at the time of testing. Excluding criteria were corneal opacities, glaucoma or other optic nerve diseases, any maculopathy other than IMH, other retinal diseases, amblyopia, or a refractive error before cataract surgery greater than 6.0 diopters spherical or 3.0 diopters cylindrical. Mean SD of last follow-up was 54 ± 20 (range 25–91) months after surgery. All patients and subjects underwent complete ophthalmic examination, including refraction and BCVA, Amsler grid, anterior segment examination, and indirect ophthalmoscopy. BCVA was assessed using a decimal visual acuity chart, and the decimal visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) units for analysis.

Spectral-Domain Optical Coherence Tomography

To analyze foveal structure and thickness of individual retinal layers, all patients and subjects were scanned with SD-OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) using the eye-tracking feature as previously described. All patients were scanned at last follow-up. Time-domain OCT (TD-OCT) was not used for the thickness measurement of retinal layers. In brief, a scan along the horizontal meridian was segmented. This scan was also used for a qualitative analysis of the integrity of the foveal photoreceptor cone outer segment tips (COST) line, the IS/OS junction, and the ELM. If more than one scan was available, the scan of the highest quality was chosen. The segmentation data are shown for 6 mm (3 mm from foveal center) for all eyes. This ensured that the same regions were compared for all patients and subjects and that the region close to the optic disc was not included (Fig. 2A). To clearly differentiate inner retinal dimples and a re-formed fovea, we defined the presence of a foveal pit as inner retinal depression without clear distinction of the retinal nerve fiber layer (RNFL), the retinal ganglion cell layer (RGC), and the inner plexiform layer (IPL) in the center of the scan (Fig. 3).

A digital image (.png) of the foveal scan was exported from the analysis window of the frequency domain OCT machine (Heidelberg Engineering). Segmentation of the retinal layers was done by hand (aided by a program written in C++, using wxWidgets GUI library and SQLite database; in the public domain at http://wxwidgets.org). Experienced operators (KP and FT) segmented each scan by marking the boundaries of the layers by clicking on points along the boundaries of interest. The program drew a curve through these points using either linear or cubic spline interpolation.

Eight boundaries were identified and labeled a through g (Figs. 2B, 2C). Using the locations of these boundaries, we identified six retinal layers and total retinal thickness: Total retinal thickness is the distance between a and g; RNFL is the distance between a and b; RGC+IPL is the distance between b and c; inner nuclear layer (INL) is the distance between c and d; outer plexiform layer (OPL) is the distance between d and e; outer nuclear layer (ONL) is the distance between e and f; photoreceptor inner and outer segment plus retinal pigment epithelium (RPE)-Bruch’s membrane (IS/OS+RPE) is the distance between f and g (Fig. 2C).

The thickness of the six layers and the total retinal thickness were calculated by computing software evaluating the interpolated boundary curves at 100 equidistant positions and calculating the vertical differences of successive boundaries.

Time-Domain Optical Coherence Tomography

TD-OCT (Stratus OCT III; Zeiss, Jena, Germany) was used for the postoperative longitudinal analysis of macular thickness because SD-OCT was not yet available when the first patients were operated. All measurements used for the postoperative longitudinal analysis of macular thickness were performed with TD-
OCT. Scanning was performed before surgery and at various times for up to 91 months after surgery (Fig. 4). The scanning protocol used for this study was the standard Fast Macular Thickness program (Stratus OCT III; Zeiss) as previously described. For the purpose of this study, the first concentric field was analyzed (Fig. 4F). Preoperative macular hole diameter was measured with either TD-OCT or SD-OCT at the narrowest midpoint.

Surgical Procedure

The standardized surgical procedure consisted of 20-gauge, three-port pars plana vitrectomy including the induction of a posterior vitreous detachment. Balanced salt solution (BSS; Alcon, Fort Worth, TX) was used as an irrigation solution. In all eyes, the ILM was engaged with intraocular forceps to create a flap and then was peeled in a circular fashion in the entire macula. BSS was exchanged with 14% $\mathrm{C}_2\mathrm{F}_6$ gas.
Results

Statistical Analysis

Reference values from normal control eyes were described by quantiles 3%, 50%, and 97% (Ref. 16 and Fig. 5). Retinal thickness measurements of individual layers of operated eyes and of normal control eyes were described by median values with 95% confidence intervals (CIs). Differences of thickness were considered significant in areas in which the CIs did not overlap (Fig. 6). Longitudinal data of retinal thickness in each subfield of the TD-OCT Fast Macular Thickness program (Fig. 4) and of BCVA (Fig. 7) were analyzed by nonlinear mixed-model regression before surgery and for up to 91 months after surgery. A reference interval (Fig. 4) was derived from the fences out of box-whisker analysis (median value and the lowest/highest value within 1.5 times the interquartile range of the lower/upper quartile) of the normal control eyes. Results were analyzed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL) and R software (R2.10), including the special package for nonlinear mixed-effects models. Correlation of preoperative macular hole size and final BCVA was calculated using Pearson’s correlation coefficient.

Results

Age of subjects ranged between 52 and 82 years with a mean of 68 ± 5 years. Mean age of control subjects was 72 ± 6 years (range 59–85). There was no statistically significant difference between the ages of study and control patients (P > 0.05, Mann-Whitney test).

Patients were operated by four different experienced surgeons. Between 2005 and 2007, 11 eyes were operated with indocyanine green (ICG), and 20 included eyes were operated without vital stains. In 2007 we stopped using ICG as a vital stain, and thereafter all eyes were operated with Brilliant Blue G (Brilliant Peel; Fluoron, Ulm, Germany). Twenty included eyes were operated between 2007 and 2009 with Brilliant Blue G. Eight eyes were pseudophakic at the time of surgery; 28 phakic eyes underwent concomitant standard small-incision phacoemulsification cataract surgery with implantation of a standard monofocal intraocular lens, and 15 eyes underwent standard cataract surgery 6 to 17 (mean 12 ± 3) months after vitrectomy.

Foveal Structure

The preoperatively obtained SD-OCT Fast Macular Thickness program showed diffuse retinal thickening around the IMH (Figs. 4A–E, 0 months). SD-OCT scans of the horizontal meridian obtained at last follow-up showed a foveal pit in 43 of 51 eyes.

Eleven eyes had circumscribed foveal or juxtafoveal defects of the COST line, the IS/OS junction, or the ELM. In three eyes, only the IS/OS junction was affected; in two eyes, only the ELM was affected. In two eyes, the COST line and the IS/OS junction were affected. In one eye, the COST line and the ELM were affected. In one eye, the IS/OS junction and the ELM were affected. In two eyes, all three structures were affected. The median curves shown in Figure 6G demonstrate that in most eyes the shape of the fovea returns to near normal long-term after surgery.

Retinal Layers Along Horizontal Meridian Long-Term After Surgery

All SD-OCT scans were oriented as if they were from left eyes; that is, the results from the right eye were plotted from the nasal to the temporal retina to match the results from the left eyes. Therefore, in Figures 5 and 6 the nasal retina (closer to the optic disc) is to the left and the temporal retina is to the right, with 0 on the x-axis indicating the center of the fovea. The data of the controls agreed with known retinal anatomy (Figs. 5, 6).

The data for the individual patient eyes are shown in Figure 5. The bold black curves are the quantiles (3%, 50%, and 97%) of the control eyes. In most eyes the curves of all retinal layers do not deviate from the 3% and 97% quantile limits (Fig. 5).

Median curves for the controls are shown in Figure 6 as the central blue line. The additional blue lines above and below the central blue line represent the 95% CIs. Median and 95% CIs for the 51 patient eyes are shown as red lines. Consistent with the results of the Fast Macular Thickness program, which showed that not all eyes had returned to normal thickness values in the central subfield (Fig. 4A), total retinal thickness was slightly increased in the fovea (Fig. 6G). The median thickness of the GCL+IPL, INL, and OPL in the fovea was greater than normal while that of the other retinal layers was normal (Fig. 6).

Postoperative Course of Macular Thickness

All five macular subfields of the TD-OCT Fast Macular Thickness program were thickened preoperatively (Figs. 4A–E, 0 months). Postoperatively, retinal thickness decreased nonlinearly in all subfields. In the central subfield it entered the reference interval derived from the normal control eyes 28 months after surgery, whereas the retinas of several eyes...
Figure 4. Longitudinal data of the TD-OCT Fast Macular Thickness program before and after IMH surgery. Longitudinal data of retinal thickness in each subfield analyzed by nonlinear mixed-model regression preoperatively (0 months) and postoperatively. The horizontal lines represent the reference interval derived from box-whisker analysis of the normal control eyes (median value and the lowest/highest value within 1.5 times the interquartile range of the lower/upper quartile). The arrows indicate the time points when the regression enters the reference interval. (A) The retinal thickness of the central subfield entered the reference interval 28 months postoperatively, while several eyes remained thickened during the entire follow-up period. (B–E) The thickness of the nasal, superior, temporal, and inferior subfield entered the reference interval 1 to 6 months postoperatively and returned to normal during the following months. (F) Five subfields of the Fast Macular Thickness program. Multiple measurements of the same value are jittered. Over the longitudinal course, the total number of visits was 177. The mean number of visits per patient was 3.5 (range 2–6).
**Figure 5.** Thickness of retinal layers along horizontal meridian long-term after surgery. RNFL (A), RGC+IPL (B), INL (C), OPL (D), ONL (E), IS/OS+RPE (F), and total retina (G) thickness curves are shown for 40 patients' eyes (colored lines). For comparison, the bold lines are the 3%, 50%, and 97% quantiles of normal control eyes. 

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Figure 6. Median thickness of retinal layers along horizontal meridian long-term after surgery in normal controls and in patients. The blue lines are median ± 95% confidence intervals for the 30 control eyes. The red lines are median ± 95% confidence intervals for the 40 patient eyes. RNFL (A), RGC+IPL (B), INL (C), OPL (D), ONL (E), IS/OS+RPE (F), and total retina (G) thickness curves are shown in separate panels.
remained thickened during the entire follow-up period (Fig. 4A).

The nasal macular thickness entered the reference interval 6 months after surgery (Fig. 4B). The thickness of the superior, temporal, and inferior subfields entered the reference interval 1 to 2 months after surgery (Figs. 4C–E). The data of the controls agreed with known retinal anatomy (Fig. 4).

**Best-Corrected Visual Acuity**

The control eyes had logMAR BCVA (Snellen equivalent) 0.1 (20/25) or better. Preoperative mean BCVA of the patients was 0.7 (20/100) ± 0.3 (3 lines) (range 1.3 [20/400]–0.2 [20/32]). One to 3 months postoperatively, mean BCVA was 0.4 (20/50) ± 0.2 (2 lines) (range 1.0 [2/20]–0.1 [20/25]). Mean BCVA was 0.35 (20/44) ± 0.2 (2 lines) three to 6 months postoperatively, 0.3 (20/40) ± 0.2 (2 lines) 1 year postoperatively, 0.2 (20/52) ± 0.2 (2 lines) 2 years postoperatively, and 0.14 (20/28) ± 0.1 (1 line) (range 0.4 [8/20]–0.0 [20/20]) after a mean follow-up of 54 ± 20 months.

**Final Best-Corrected Visual Acuity and Foveal Structure**

High-level BCVA of logMAR (Snellen equivalent) 0.05 (20/22.5) to 0.0 (20/20) was achieved at last follow-up by 11 of 43 eyes with foveal pit and by 4 of 8 eyes without foveal pit. Mean BCVA at last follow-up of all 8 eyes without foveal pit was 0.1 (20/25) ± 0.1 (1 line) (range 0.3 [20/40]–0.0 [20/20]).

**Final Best-Corrected Visual Acuity and Macular Hole Size**

Mean preoperative size of macular hole at the narrowest midpoint was 300 μm (range 137–748 μm). Size of macular hole and final BCVA did not correlate significantly (Pearson 0.174, P = 0.28).

**Final Best-Corrected Visual Acuity of Patients Who Refused Follow-Up Visit**

Twenty-seven patients who refused the scheduled visit were not included in the analysis shown in Figures 4 through 7. We obtained last visual acuity from their local ophthalmologists. Mean last BCVA was logMAR (Snellen equivalent) 0.17 (20/30) ± 0.1 (1 line) (range 0.5 [20/63]–0.0 [20/20]) obtained at a mean of 52 ± 23 months (range 9–86 months) postoperatively. Visual acuity was assessed without refraction in 5 of 27 patients.

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**Figure 7.** Longitudinal data of best-corrected visual acuity (BCVA) analyzed by nonlinear mixed-model regression before IMH surgery (0 months) and postoperatively. Multiple measurements of the same value are jittered. Over the longitudinal course, the total number of visits was 178. The mean number of visits per patient was 3.5 (range 2–6).
Amsler Grid
No patient described pronounced distorted lines. Thirty-seven patients described mildly distorted lines, while 14 patients described no distortion.

Indocyanine Green, Brilliant Blue G, or No Vital Stain
There was no apparent difference in final BCVA, thickness of retinal layers, or the nonlinear mixed-model regression analysis of the postoperative course of BCVA or of central macular thickness between eyes operated without vital stain or with Brilliant Blue G (data not shown). Mean final BCVA was better when 11 eyes operated with ICG were excluded from the analysis 0.1 (20/25) ± 0.1 (1 line) (range 0.4 [8/20]–0.0 [20/20]) vs. 0.14 (20/28) ± 0.1 (1 line) (range 0.4 [8/20]–0.0 [20/20]). There was no apparent difference in thickness of retinal layers or of central macular thickness between 11 eyes operated with ICG and 40 eyes operated either without vital stain or with Brilliant Blue G (data not shown).

DISCUSSION
The main findings of this study are, first, that long-term postoperatively, the median thickness of the RGCþIPL, INL, and OPL in the fovea remained slightly greater than normal while that of all other retinal layers was normal. The median foveal shape of the entire retina was slightly distorted (Fig. 6). Second, postoperatively, central macular thickness gradually decreased (Fig. 4A), which appears to be related to a gradual functional improvement over a period of several years (Fig. 7).

The control individuals were of similar age distribution because slight age-related retinal thinning in normal eyes has been described.20 Analysis of the thickness measurements derived from 51 operated eyes allows the observation of trends. Long-term after surgery, the retinal thickness of the peripheral macula returned to normal (Fig. 4B–E) while the decrease of the thickness of the foveal area toward normal values was incomplete and delayed (Fig. 4A). To analyze the morphology of the retina more specifically and to depict the microstructure of the fovea more accurately, we used SD-OCT scans as previously described by Hood et al.21 and previously adapted by us.16 SD-OCT showed, in line with the results of the TD-OCT Fast Macular Thickness program, that the decrease of total retinal thickness along the horizontal meridian in the fovea remained incomplete, with slightly greater thickness of the nasal part of the fovea and parafovea compared to the temporal part (Figs. 5G, 6G). This is in accordance with the findings of another OCT study22 and our findings long-term after epiretinal membrane surgery.16 Small differences in thickness measurements of individual retinal layers must be interpreted with caution because mild deviations of SD-OCT scans from the exact anatomic horizontal meridian may have introduced small errors.

Kim et al. have recently reported an elongation of foveal tissue 6 months after IMH surgery with a mean horizontal distance between the parafoveal edge of the OPL (inter-OPL distance) of 575.4 ± 94.8 μm.15 This is in contrast to our findings, perhaps because of the longer follow-up period in our study. As shown in Figure 6G, the median horizontal shape of the fovea was not elongated as compared to the normal control eyes. We found an elongated fovea only in 4 of 51 eyes with horizontal inter-OPL distances of 572, 580, 723, and 751 μm.

In accordance with other studies,16,23 the mild irregular shape of the retinal layers and the absence of a foveal pit (Fig. 3) did not preclude favorable long-term postoperative visual acuity. Overall, in the present study, BCVA continuously improved postoperatively and reached good levels in most patients (Fig. 7).

It is unclear why the decrease of central macular thickness was delayed to 28 months postoperatively, but this appears to be related to gradual functional improvement (Figs. 4A, 7). The mean follow-up time in the present study was considerably longer than in other studies.1–4,6–13 However, further postoperative decrease of central macular thickness after the follow-up period of this study cannot be excluded.

Preoperative macular hole size has been described as a prognostic factor for functional outcome related to a correlation of closure rate and hole size.22 We did not find a correlation of macular hole size and final BCVA, probably because we included only macular holes successfully closed after one surgery.

There are limitations of this study. We found good long-term functional and anatomical outcome, and this is in part due to the long follow-up period (Figs. 4, 7). However, due to the patient selection process (Fig. 1), bias toward eyes with better outcome cannot be entirely ruled out. ICG-related phototoxicity24 may have influenced the functional and anatomical outcome of macular hole surgery in 11 eyes operated with ICG, and more “difficult” cases may have been operated with the aid of ICG between 2005 and 2007. However, we did not find a clear difference between the eyes operated without ICG between 2005 and 2007 and those operated with Brilliant Blue G between 2007 and 2009, although we did not apply statistical tests because of the limited number of eyes in each subgroup. Twenty-seven patients who refused the scheduled visit (Fig. 1) represent a second potential source of bias. These patients may have refused the visit because of unfavorable outcome. However, this seems unlikely because the last obtained visual acuity of these patients was similar to that of the included study patients, although 5 of 27 patients had not been refracted.

In conclusion, the mean long-term functional outcome of macular hole surgery with ILM peeling is excellent, and the microstructure of the fovea recovers almost completely in most eyes. Long-term follow-up periods are warranted because the process of gradual functional and anatomical recovery after IMH surgery may continue for several years after macular hole surgery.

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References


